REMARKS

The Official Action dated March 11, 2004 has been carefully considered. Accordingly, the amendments and remarks presented herein are believed sufficient to overcome the rejections of the Examiner and place the present application in condition for allowance. As these amendments are not believed to constitute new matter, Applicants believe that entry is in order and is therefore respectfully requested. Claims 1-64 are currently pending and claims 1-22, 30-44 and 63 are under examination.

First, Applicants acknowledge and appreciate the Examiner's corrections of minor errors in the Information Disclosure Statement.

Specification Comments

The Examiner noted that the present specification employs some trademarks, and commented as to the necessity for proper proprietary use of trademarks. While Applicants understand that capitalization suffices to conform to appropriate trademark use, Applicants note that their use also conforms, as the present specification clearly uses the TM designator to inform the reader of trademark status (see page 61, line 29 for ImageQuant™, page 62, line 8 for Prizm™, page 58, line 4 for Quiaquick™) Further, Applicants employed proper use of the trademarks as adjectives modifying the generic product, e.g. Prizm™ software. To the extent Applicants used Corporate names as sources of material, they did not designate them as trademarks. Applicants are unclear as to whether the Examiner's comments constituted an objection of the specification as filed or a stated preference for a form of trademark designation. Applicants will be glad to conform to any such form if the Examiner indeed objects to the specific form employed by Applicants.

Claim Objections

Claims 12 and 21 were objected to due to the informality of the phrase "random amplification DNA." The Examiner requested appropriate correction. As per the Examiner's suggestion, the claims have been amended so that the claims recite the phrase "random amplification of DNA." Hence, the objection has been overcome and reconsideration is respectfully requested.

Drawings

Corrected drawing sheets are submitted herewith for Figures 1-4 as submitted on October 19, 2000 and March 20, 2003, and approved by the Examiner.

35 U.S.C. § 112, second paragraph

Claims 1-22, 30-44 and 63 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. First, the Examiner asserts that claims 1-5 are indefinite because it is unclear as to whether the claims merely require detection of a polymorphic site, as indicated by the final step of claim 1, or whether the claims require that detection of a polymorphic site determines "alpha-2B-adrenergic receptor function," as recited in the preamble of claim 1. The Examiner further asserts that the claims do not make it clear how detection of a polymorphic site would allow one "to determine alpha-2B-adrenergic receptor function."

Independent claim 1 and dependent claims 2-5 were amended to clarify the inventive methods. Independent claim 1 is directed to a method of determining alpha-2B-adrenergic receptor function by detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2B-adrenergic receptor molecule. The method comprises: (a) obtaining a sample of a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising

SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide; and (b) detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof.

Applicants appreciate the Examiner's observations that the language was confusing and believe that the amendment to claim 1 clarifies that the aspect of the invention defined by claims 1-5 provides a method for determining alpha-2BARs functioning based on the detection of a polymorphism in a specific polymorphic site in a polynucleotide encoding the alpha-2BAR. The specification (page 9-10, e.g.) discloses a correlation of particular alpha-2BAR polymorphisms to specific alterations in function. Hence, the rejection is overcome and reconsideration is respectfully requested.

In addition, the Examiner asserts that several claims are indefinite for lack of a proper antecedent basis to certain recited limitations. Specifically, the Examiner asserts that claims 1-5 are indefinite for lack of an antecedent basis to the recited limitation "the sample having a polynucleotide." Claims 5 and 11 were also rejected for a lack of antecedent basis for the limitation "the complement of the polymorphic site." Claims 16-22 were rejected for lack of an antecedent basis to "the sample having a polynucleotide," "the alpha-2B adrenergic receptor molecule," "the oligonucleotide," "the incubation," and "the hybridization." Claim 63 was rejected for lack of proper antecedent basis for "the sample having a polynucleotide..." and "the polymorphic site comprising..." Applicants appreciate the Examiner's critique and suggestions and believe that proper antecedent bases now exist throughout the currently amended claims for all the recited limitations and respectfully request reconsideration.

Further, the Examiner asserts that claims 1-5 are indefinite over the recitation of the language "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof." Specifically, the Examiner asserts that it is unclear what might constitute a site comprising particular "nucleotide positions" of a recited SEQ ID NO., and suggests that reference to a "molecule" might be more accurate. This rejection is traversed and reconsideration is respectfully requested. In addition, the Examiner asserts that it is unclear as to what the recitation "fragment or complement thereof" refers.

First, Applicants note that the assertedly indefinite passage now reads "a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof." Applicants submit that the term "polymorphic site" is used consistently throughout the disclosure and amended claims to specify by position that portion of a nucleotide sequence which co-exists in more than one form in a species population (e.g. page 12, paragraph 2). "Polymorphism" is defined in the present specification on page 13, lines 3-4. The specification specifically discloses how to identify a "polymorphism or polymorphic site" in the alpha-2BAR receptor. How to identify and locate a particular polymorphic site designated by nucleotide sequence positions is disclosed in detail on pages 14 and 15, paragraphs 5 and 1 respectively, and several embodiments are provided on pages 15-17. Finally, Applicants note that the term "fragment" is specifically defined on page 16, first full paragraph, as referring to less than the entire nucleotide sequence of SEQ ID NO: 1 or 2, with a preferred fragment comprising the nucleotides at positions 901-909 of SEQ ID NOs: 1 or 2. Applicants believe that the intended meaning of this recitation is clear and definite and the rejection has been overcome. Reconsideration is respectfully requested.

Claim 3 was rejected as being indefinite due to the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Specifically, the Examiner notes that the claim refers to 9 different nucleotide positions, and inquires whether the claim is intended to require an insertion at each of these positions, a single insertion of 9 nucleotides within this region, replacement of these 9 nucleotides, and so on. Further, the Examiner asserts that the language "polymorphic site is an insertion" is indefinite, since it is not clear whether this language refers to a site at which an assertion may occur, or to a fragment or sequence that is inserted at a particular site. The Examiner notes that "a 'polymorphic site' is a location within a molecule, not a molecule per se." Finally, the Examiner asserts that it is unclear as to whether the claim requires a polynucleotide comprising SEQ ID NO: 1, and, if not, it is unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1 might be located or identified.

Applicants submit that the amendment to claims 1, 2 and 3 resolve the asserted lack of clarity with respect to the intended meaning of the claim terms. When read in light of the specification at pages 10 and 11, it is clear that the insertion polymorphism cited in claim 3 comprises the nucleotide sequence 901-909 in SEQ ID NO:1. This sequence encodes the wild-type receptor (see page 11, paragraph 2), and the "insertion" designates the presence of the nine nucleotides disclosed at positions 901-909 of SEQ ID NO: 1, the absence of which defines the variant disclosed by SEQ ID NO: 2. Hence, the scope of a method wherein the polymorphism is an insertion of 9 nucleotides at nucleotide positions 901-909 of SEQ ID NO:1 is definite and Applicants respectfully submit that the rejection should be withdrawn.

The Examiner also found claim 4 to be indefinite for similar reasons. First, the Applicants point out that the Examiner misread claim 4 as reciting SEQ ID NO: 1, when, in fact, claim 4 recites "wherein the polymorphism *is* a deletion of 9 nucleotides at nucleotide

positions 901 to 909 of SEQ ID NO: 2." Applicants also point to the specification at page 10 and page 15, paragraph 2 wherein it is clear that SEQ ID NO:2 has a deletion of 9 nucleotides when compared to the wild type (SEQ ID NO:1) at positions 901-909. Applicants note that the terms "insertion" and "deletion" in the context are relative, but stress that they are designations well known and understood in the art to refer to polymorphisms which manifest a presence or absence of particular nucleotides, respectively. Hence, the claim is definite and the rejection has been overcome. Reconsideration is respectfully requested.

The Examiner rejected claims 6-12 as being indefinite, "because it is unclear as to whether the claims are actually drawn to a method that results in "genotyping" as recited in the preamble." The Examiner maintains that claim 6 merely requires detection of a polymorphic site rather than a sequence so that it is unclear how the method steps recited would result in "genotyping." Second, the Examiner rejected claims 6-12 as indefinite over the recitation of the language "a polymorphic site comprising nucleotide positions 901-909 of SEQ ID NO: 1 or 2 or a fragment or a complement thereof," and requires clarification as to several related issues.

Applicants appreciate the Examiner's confusion and have amended claim 6 to clarify that the method comprises, inter alia, detecting "a polymorphism at a polymorphic site" and not merely detecting a polymorphic site, per se. In addition, Applicants point out that "nucleotide positions 901-909 of SEQ ID NO:1" provides a reference point that is precisely identified, and the claim language has been amended to clarify the reference for a fragment and a complement. Hence, the rejection has been overcome and reconsideration is respectfully requested.

The Examiner rejected claim 9 as being indefinite over the recitation "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Instant dependent claim 9 recites "wherein the polymorphism is an insertion of 9

nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1." Applicants submit that the term "insertion" in this context makes it clear to a person of ordinary skill in the art that there are 9 nucleotides present in the recited polymorphism as compared to other forms, and that these 9 nucleotides are present at positions 901-909 of SEQ. ID NO: 1. Hence, the scope of instant claim 9 is defined and reconsideration is respectfully requested.

The Examiner rejected claim 10 as indefinite over the recitation of "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Applicants note that instant claim 10 recites "wherein the polymorphism is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 2." Applicants submit that the meaning of the term "deletion" with respect to one form of a polymorphism that is lacking specified nucleotides compared with other polymorphic forms is clear in this context to a person of ordinary skill in the art. Specifically, it is clear that the polymorphic form recited in claim 10 has a different 9 nucleotides at positions 901 to 909 due a deletion of 9 nucleotides when compared to other polymorphic forms. Hence, the rejection is overcome and reconsideration is respectfully requested.

The Examiner rejected claims 13-15 as being indefinite because it is assertedly unclear as to whether the claims are actually drawn to methods of genotyping a polynucleotide since the single step of claim 13 "merely requires 'performing a primer extension reaction' using an oligonucleotide." This rejection is traversed.

Applicants submit that the transitional language "comprising" implies that other steps may be taken in addition to those steps explicitly recited. In the present case the implied steps are well-known in the art and a person of ordinary skill in the art would recognize that the recited step imparts novelty to otherwise well-known methods. In addition, instant claim 13 also requires obtaining a sample comprising the polynucleotide. Further, it is clear that requisiteoligonucleotide comprises at least one nucleotide comprising a nucleotide sequence

homologous to a nucleotide sequence located at positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof. Reconsideration is therefore respectfully requested.

Claim 14 was rejected as being indefinite over the recitation of the language "wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50 nucleotides." Specifically, the Examiner asserts that an oligonucleotide by definition is composed of nucleotides, so that it is unclear how the language of claim 14 further limits the oligonucleotide of the claim. Applicants appreciate the observation and note that instant claim 14 recites wherein the oligonucleotide comprises a nucleotide sequence having a length of from about 10 to about 50 nucleotides. As this language clearly limits the oligonucleotides recited in claim 13, Applicants submit that the rejection is overcome and reconsideration is respectfully requested.

Claims 16-22 were rejected as being indefinite "because it is unclear whether the claims are drawn to a 'method of genotyping a polynucleotide' as recited in the preamble of claim 16, or to a method of obtaining 'the genotype of an individual', as recited in the final process step. Applicants note that claim 16 is now clearly directed to a method of "genotyping an individual by genotyping a polynucleotide," and submit that

Claims 16-22 are further rejected as indefinite because "it is not clear whether the recitation 'fragment or complement thereof' refers to a fragment or complement of the previously recited 'polynucleotide,' or whether this language indicates that fragments and complements of SEQ ID NOs. 1 and 2 are considered to encode alpha-2B adrenergic receptor molecules." Applicants note that instant claim 16 recites "a fragment of a complement of the polynucleotide," which is precise with respect to the object of the preposition at issue. Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claims 16-22 were additionally rejected as indefinite over the recitation of the phrase "identifying the polymorphic site to obtain the genotype of the individual" in step (d).

Specifically, the Examiner asserts that it is unclear how the identification of a "polymorphic site" would allow one to determine an individual's genotype. Applicants submit that step (d), which now specifies that the polymorphic site comprises a particular polymorphism clarifies the inventive method and overcomes this rejection. Reconsideration is respectfully requested.

Claims 16-22 were also rejected as indefinite over the recitation of the phrase "wherein the polymorphic site comprises an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NOs: 1 or 2" in claim 16. Specifically, the Examiner asserts that it is unclear whether the claim intends to require an insertion at each of the nine positions, a single insertion or deletion of 9 nucleotides within this region, replacement of these 9 nucleotides with 9 different nucleotides, etc. The Examiner further asserts that the claim as written does not require SEQ 1 or 2 but only a fragment of complement and it is unclear how the claimed method may be practiced in the absence of SEQ ID NO: 1 or 2.

Applicants note that claim 16 now recites "wherein the polymorphic site comprises a polymorphism comprising an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2..." Hence it is clear that the recited insertion or deletion is of the nucleotides constituting polymorphism located at the specified polymorphic site. Noting that since there are 9 nucleotide positions at a site defined as positions 901 to 909, and that the claimed method requires an insertion or deletion of 9 nucleotides at that position, then all nine nucleotide positions are implicated in this step. Applicants draw the Examiner's attention to the difference in the total nucleotide length between SEQ ID NO: 1 and NO: 2, which is 1353 versus 1344 nucleotides, respectively, which is a total of 9 nucleotides difference. Applicants submit that the aforementioned clarifications as to claims 16-22 overcome all the asserted grounds of indefiniteness and respectfully request reconsideration.

Claim 17 was rejected as being indefinite over the recitation "amplifying the polymorphic site of the polynucleotide." Applicants appreciate the Examiner's confusion and submit that any lack of clarity has been resolved by reciting that amplification is of the polymorphism, not of the polymorphic site, per se. Hence, the claim language is rendered clear and definite and Applicants respectfully request reconsideration.

Claim 18 was rejected as indefinite over the inclusion of SEQ ID NOs: 17-18 in the claim. Specifically, the Examiner asserts that claim 16 requires an oligonucleotide "having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of the nucleotide present at a polymorphic site of the polynucleotide," but that SEQ ID NOs 17 and 18 are identified in the specification as being primers that specifically hybridize to M13 vectors, not to a polymorphic site, so that it is unclear as to how or whether SEQ ID NOs. 17 and 18 might function in the methods of the claims as presently written. This rejection is traversed and reconsideration is respectfully requested.

Applicants draw the Examiner's attention to page 57 of the specification wherein a polymorphism detection is exemplified. The sequences identified as SEQ ID NOs: 17 and 18 are disclosed as corresponding to the M13 forward and reverse, respectively, and are also disclosed as being universal sequencing primers. In fact, it is disclosed that the 5' end of each sense and antisense primer contained these sequences, respectively. Hence, these primers may behave as the "at least one oligonucleotide having a nucleotide sequence that is complementary to a region of the polynucleotide" which permit identification of the nucleotide present at the polymorphic site of the polynucleotide, and it is therefore appropriate to include them in the Markush group of claim 18. Reconsideration is respectfully requested.

Claim 22 was rejected as being indefinite over the recitation of the language "wherein the oligonucleotide comprises a nucleotide sequence from about 10 to about 50 nucleotides," as the Examiner asserts that it is unclear how this further limits the oligonucleotides of the claim. Applicants appreciate the Examiner's suggestion and have incorporated so that claim 22 now recites "wherein the oligonucleotide is from about 10 to about 50 nucleotides in length." Hence, the ground for indefiniteness has been overcome and reconsideration is respectfully requested.

Claim 30 was rejected as being indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof." Specifically, the Examiner asserts that it is not clear whether the claim encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or whether the claim encompasses a polymorphic site comprising positions 901-909 of a "fragment or complement" of SEQ ID NO: 1 or 2. Further, the Examiner asserts that to the extent the claims encompass polynucleotides that do not include either SEQ ID NO: 1 or 2, it is not clear how the nucleotide positions required by the claims would be identified.

Claim 30 is also rejected as being indefinite over the recitation " determining the identity of an additional polymorphic site." Specifically, the Examiner asserts that it is not clear whether this language refers to determination or detection of a polymorphism or to determination of another "site" at which a polymorphism is known to be located or whether the claim encompasses identification of an additional site as being polymorphic.

Applicants note that instant claim 30 is directed to a method of haplotyping an alpha-2B-adrenergic receptor gene, wherein the gene exists as a first copy and a second copy, the method comprising: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement

of the polynucleotide; b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof on a first copy of the alpha-2B-adrenergic receptor gene; and c. determining the identity of an additional polymorphic site on the first copy of the alpha-2B-adrenergic receptor gene. Hence, the object of the ambiguously recited prepositional phrase has been clarified.

With respect to the second grounds of asserted indefiniteness, Applicants point the Examiner to the specification at page 15, first full paragraph, which describes a specific polymorphism as a nine nucleotide base insertion which *is* a polymorphic site or fragment. Applicants appreciate the confusion stemming from the interchanging uses of these terms, however , it is clear from this description that while a polymorphic site precisely refers to a position, it is always the location of particular polymorphisms. Hence, in the presently recited method claims, detection of a polymorphic site is detection of a polymorphism and vice versa, and claim 30 thus requires determining the identity of an additional polymorphic site, which implies identification also of an additional polymorphism. Applicants submit that the claim language is definite in light of the specification and reconsideration is therefore respectfully requested.

Claims 31-37 were rejected as being indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease." Specifically, the Examiner asserts that it is not clear whether the claim encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or a polymorphic site comprising positions 901-909 of a "fragment of complement" of SEQ ID NO: 1 or 2. The Examiner further asserts that to the extent the claims do not encompass SEQ ID NO 1 or 2, it is not clear how one would identify these positions in a fragment or complement. Also, the

Examiner asserts that it is unclear whether the phrase "which correlates to the disease" refers back to the polymorphic site, to SEQ ID NO 1 or 2 or fragment or complement thereof, to only the fragment or complement thereof, etc.

Applicants note that present claim 31 is directed to a method for identifying an individual at increased risk for developing a disease associated with an alpha-2B-adrenergic receptor molecule comprising: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide from the individual; and b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof, wherein the polymorphism correlates to the disease, thereby identifying the individual at increased risk for the disease.

From this recitation it is clear that a polymorphism is at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof." Further, Applicants note that claim 31 now clearly specifies, as taught in the specification at page 47 in the second full paragraph, that it is the specific polymorphism which may correlate to a disease. Hence, Applicants submit that claim 31 and claims 32-37 which depend therefrom are clear and definite in scope and respectfully request reconsideration.

Claim 34 was rejected as being indefinite over the recitation "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Specifically, the Examiner asserts that it is unclear as to whether the claim is intended to require an insertion at each of these positions, etc. Further, the Examiner asserts that the language "polymorphic site is an insertion" is indefinite because a polymorphic site is a location within a molecule, not a molecule, per se. Also, the Examiner asserts that it is

unclear how "nucleotide position 901 to 909 of SEQ ID NO: 1 might be located or identified if a polynucleotide comprising SEQ ID NO 1 is not required by the claims.

Claim 35 was rejected as being indefinite over the recitation of the language "wherein the polymorphic site is a deletion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1. Specifically, the Examiner notes that a polymorphic site is a location within a molecule ad not a molecule per se, and that it is unclear whether claim 35 requires a polynucleotide comprising SEQ ID NO: 1, and, if not, how this position would be either located or identified.

As the rejection bases and responses are similar, the asserted indefiniteness of claims 34 and 35 will be addressed together. First, Applicants note that both instant claims are directed to methods wherein the polymorphism is an insertion (claim 34)/ deletion (claim 35) of 9 nucleotides at nucleotide positions 901 to 902 of SEQ ID NO: 1 (claim 34) / SEQ ID NO: 2 (claim 35). Applicants submit that it is clear in light of the specification and with the knowledge typical of one skilled in the art that the polymorphism which is an insertion at nucleotide positions 901-909 reflects the presence of a 9 nucleotide sequence not found in the polymorphism which is a deletion of 9 nucleotides at nucleotide positions 901- 909. Applicants admit to some potential for confusion due to the shifting reference frame, as insertion in SEQ ID NO: 1 is as compared to SEQ ID NO: 2, while deletion in SEQ ID NO: 2 is as compared to SEQ ID NO: 1, but that the specification makes resolution and comprehension of the intended scope clear. (See page 15, paragraph 2 describing SEQ ID NO: 2, page 14, paragraph 2 describing SEQ ID NO. 1 and page 14, paragraph 4 describing polymorphisms in both sequences, e.g.). In addition, Applicants appreciate the Examiner's concern with the use of "polymorphic site" to intend a polymorphism and have amended the claims accordingly. Hence, the rejection is overcome and reconsideration is respectfully requested.

Claim 36 was rejected as indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6," due to both an insufficient antecedent basis and lack of clarity with respect to how "polymorphic site" is used and as to what would constitute a "complement thereof." Applicants note that instant claim 36 is directed to the method according to claim 33 wherein the complement of the polymorphism comprises SEQ ID NO: 5 or 6. Hence, proper antecedent bases exist for both the complement and the polymorphism, and the term "polymorphism" more precisely describes the claimed method. Applicants submit that these changes overcome the rejection and reconsideration is respectfully requested.

Claims 38-44 were rejected as indefinite over the recitation of the phrase "a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or fragment or complement thereof which correlates to the disease, thereby diagnosing or prognosing the disease." Specifically, the Examiner asserts it is not clear whether the claim

encompasses a site comprising a "fragment or complement" of positions 901-909 of SEQ ID NO: 1 or 2, or whether the claim encompasses a polymorphic site comprising positions 901-909 of a "fragment or complement" of SEQ ID NO: 1 or 2. Further, the Examiner asserts it is not clear how one would identify the required nucleotide positions if SEQ ID NOs: 1 or or 2 are not required by the claims. Additionally, the Examiner asserts that it is unclear as to whether the polymorphic site, the identified sequence, or the fragment or complement "correlates to the disease." Finally, the Examiner asserts that the language does not make it clear how detection of a polymorphic site relates to prognosis of a disease.

Instant claim 38 is directed to A method for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule, comprising: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor

molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide from the individual; and b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof which correlates to the disease, thereby diagnosing or prognosing the disease.

Applicants submit that the restatement of "fragment," and the addition of the language " a polymorphism at a polymorphic site," resolve the clarity issues recited by the Examiner with respect to what is being correlated, what is required by the claims, and what relates back to the polymorphism. With respect to prognosis, Applicants note that The American Heritage College Dictionary, Third Edition, Houghton Mifflin Co. 1997, at page 1093, includes as a definition of "prognosis" as "the likelihood of recovery from a disease." Applicants submit that knowledge of the genetic origin of diseases such as cardiovascular disease, and the treatment regimens that would be accordingly considered, would be highly useful in prognosticating the disease.

Claim 41 is additionally rejected for being indefinite over the recitation of the language "wherein the polymorphic site is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Specifically, the Examiner asserts that it is unclear whether the claim requires a single insertion of 9 nucleotides or insertion at each position or so on. The Examiner further asserts that the language "a polymorphic site is an insertion" is indefinite as a polymorphic site is a location. Finally, the Examiner asserts that it is unclear as to how nucleotide positions 901-909 would be identified if SEQ ID NO: 1 is not required by the claim. Claim 42 is rejected as being indefinite for similar reasons except that it is directed to a deletion rather than insertion of nucleotides.

Instant claim 41 is directed to the method recited in claim 38 wherein the polymorphism is an insertion of 9 nucleotides at nucleotide positions 901-909 of SEQ ID

NO: 1. Instant claim 42 is identical to claim 41 except that it is directed to a deletion of 9 nucleotides in SEQ ID NO: 2.

With respect to both instant claim 41 and instant claim 42, Applicants submit that it is clear in light of the specification and with the knowledge typical of one skilled in the art that the polymorphism which is an insertion at nucleotide positions 901-909 reflects the presence of a 9 nucleotide sequence not found in the polymorphism which is a deletion of 9 nucleotides at nucleotide positions 901- 909. Applicants admit to some potential for confusion due to the shifting reference frame, as insertion in SEQ ID NO: 1 is as compared to SEQ ID NO: 2, while deletion in SEQ ID NO: 2 is as compared to SEQ ID NO: 1, but that the specification makes resolution and comprehension of the intended scope clear. (See page 15, paragraph 2 describing SEQ ID NO: 2, page 14, paragraph 2 describing SEQ ID NO. 1 and page 14, paragraph 4 describing polymorphisms in both sequences, e.g.). In addition, Applicants appreciate the Examiner's concern with the use of "polymorphic site" to intend a polymorphism and have amended the claims accordingly. Hence, the rejection is overcome and reconsideration is respectfully requested.

Claim 43 was rejected as being indefinite over the recitation of the limitation "the complement of the polymorphic site comprises SEQ ID NO: 5 or 6," for assertedly lacking proper antecedent basis and because it is unclear as to what would constitute a complement of a location.

Instant claim 43 is directed to the method recited in instant claim 40, wherein the complement of the polymorphism comprises SEQ ID NO: 5 or 6. Applicants point out that both of the Examiner's bases for rejection have been mooted and reconsideration is therefore respectfully requested.

Claim 63 was rejected as being indefinite because "it is unclear a to whether the claim merely requires indirect detection of a polymorphic site, as indicated by the final step, or

whether the claim requires that detection of a polymorphic site determines 'alpha-2B-adrenergic receptor function' as recited in the preamble. Claim 63 was further found to be indefinite due to asserted lack of clarity as to whether the claims encompass any polymorphic site located at positions 901 - 909 of any molecule, or detection of a particular sequence of nucleotides located, e.g. in SEQ ID NO: 1 or 2. The Examiner also found claim 63 to be indefinite due to lack of clarity as to what "fragment or complement thereof" relates back. Finally, the Examiner found claim 63 to be indefinite because, "to the extent the claims encompass polynucleotides which do not include either SEQ ID NO: 1 or 2, it is not clear how the particular nucleotide sequences required by the claims would be identified.

Instant claim 63 is directed to a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2B-adrenergic receptor molecule, the method comprising: a.obtaining a sample comprising a polynucleotide encoding an alpha-2B-adrenergic receptor molecule, wherein the polynucleotide or a fragment or a complement thereof comprises SEQ ID NO: 1 or 2; and b. indirectly detecting in the sample the polymorphism at the polymorphic site comprising at least one of nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof.

Applicants submit that the language of instant claim 63 on its face resolves the lack of clarity asserted by the Examiner. Hence, the rejection of claim 63 is overcome and respectfully request reconsideration.

In summary, Applicants submit that the various changes to the claim language particularly delineated above with respect to each asserted clarity or scope issue, in light of the related comments, have overcome the rejections of claims 1-22, 30-44 and 63 under 35 U.S.C. § 112, second paragraph, and reconsideration is therefore respectfully requested.

35 U.S.C § 102

Claims 1-17, 19-22, 30-44 and 63 were rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent Application Serial No. 2001/0016338 A1 to Snapir ("Snapir"), having an effective filing date of October, 1999. Specifically, the Examiner asserts that Snapir discloses detection of a common variant form (SEQ ID NO: 1) of the human α2BAR gene (SEQ ID NO: 3) wherein the variant gene encodes a receptor protein (SEQ ID NO: 2) with a deletion of 3 glu's (amino acids 307-309 of SEQ ID NO: 4), from a glu repeat element of 12 glutamates, amino acids 298-309 in the acid stretch of 18 amino acids 294- 311 of SEQ ID NO: 4, located in the 3rd intracellular loop of the receptor polypeptide. The Examiner asserts that this deletion corresponds to nucleotides 901-909 of instant SEQ ID NO: 1 as compared to instant SEQ ID NO: 2, and is therefore encompassed by the instant claims. The Examiner further asserts that Snapir's polymorphic site comprises instant "SEQ ID NO: 3 or 4 or a complement thereof, and that the complement of the polymorphic site comprises instant SEQ ID NO: 5 or 6 and additionally asserts that it is an inherent property of the receptor taught by Snapir that it comprises instant "SEQ ID NO: 7 or 8 or a fragment thereof.

This rejection is traversed and reconsideration is respectfully requested.

Instant claim 1 is directed to a method of determining α2BAR function by detecting a polymorphism at a polymorphic site in a polynucleotide encoding an α2BAR molecule. The method comprises: (a) obtaining a sample of a polynucleotide encoding an α2BAR molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement thereof, and detecting in the sample a polymorphism at a polymorphic site comprising nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a fragment or a complement thereof.

Applicants respectfully submit that the Examiner misconstrued the nucleotide positions of the polymorphism disclosed by Snapir, and therefore misinterpreted the α2BAR variant disclosed by Snapir as equivalent to the α2BAR variant instantly disclosed and

described by instant SEQ ID NO: 2. Normal wild-type human α2BAR is given as SEQ ID NO: 3 in Snapir, and SEQ ID NO: 1 in the present application. Applicants point out that these two sequences, as expected, are identical. A close inspection of the Snapir variant, SEQ ID NO: 1, and the present variant, SEQ ID NO: 2, however, reveals that they are indeed different. Both are 1344 nucleotides in length and both involve a 3-nucleotide deletion, but the deletion in Snapir is from positions 967-965, and the instant deletion is from positions 901 to 909.

The remainder of the claims rejected on the basis of Snapir, include recitation of or dependency on the limitation of a polymorphism at the polymorphic site defined by nucleotide positions 901-909 of present SEQ ID NO: 1 or 2.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Moreover, "It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it." *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research*, 68 USPQ2d 1373 (Fed. Cir. 2003). The focus should be on determining what compositions are specifically described by the reference. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). "In *Petering*, the court found that a broad generic description of compounds in a reference which encompassed the claimed compounds did not *describe* the claimed invention within the meaning of 35 U.S.C. Section 102(b)." *Ex Parte Lee*, 31 USPQ2d 1105, (Bd. Pat. App. & Int. 1993). Snapir fails to have sufficiently disclosed or enabled the polymorphism employed in the instant methods, and therefore fails to anticipate the instant method claims, 1-17, 19-22, 30-44 and 63. Hence, the rejection under 35 U.S.C. § 102 (e) has been overcome and reconsideration is respectfully requested. .

35 U.S.C. § 103

Claim 18 was rejected under 35 U.S.C. § 103 as being unpatentable over Snapir in view of Baldwin et al. (American Journal of Hypertension 12:853-857 [9/1999] ("Baldwin") and Newton ("Chapter 6: Primers" in PCZR Essential Data, C.R. Newton, ed., John Wiley & Sons, Chichester, 1995, pages 49-56). Specifically, the Examiner asserts that Snapir discloses detection of a "common variant form (SEQ ID NO:1) of the human α2B-AR gene (SEQ ID NO: 3)," which variant gene "encodes a receptor protein (SEQ ID NO:2) with a deletion of 3 glutamates, amino acids 307-309, from a glutamic acid repeat element of12 glutamates, amino acids 298-309, in an acidic stretch of 18 amino acids 294-311 (SEQ ID NO:4), located in the 3rd intracellular loop of the receptor polypeptide. The Examiner further asserts that the deletion disclosed by Snapir "constitutes a deletion of 9 nucleotides corresponding to nucleotides 901-909 of instant SEQ ID NO: 1 as compared to instant SEQ ID NO: 2 and is therefore encompassed by the instant claim. The Examiner notes that Snapir does not disclose the use of a primer consisting of present SEQ ID NO: 13 or a complement thereof and goes on to describe the elements disclosed by the secondary references with respect to that deficiency. This rejection is traversed and reconsideration is respectfully requested.

Instant claim 18 depends from instant claim 16, which is directed to a method of genotyping a polynucleotide encoding an α2B-AR molecule from a sample of an individual. The method of independent claim 16 comprises, *inter alia*, subjecting the polynucleotide to an incubation with at least one oligonucleotide having a nucleotide sequence that is complementary to a region of the polynucleotide, and identifying the polymorphic site to obtain the genotype of the individual wherein the polymorphic site comprises a polymorphism comprising an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2. Dependent claim 18 recites a Markush listing of oligonucleotides which may be employed in the method of claim 16.

However, Applicants respectfully note, as fully detailed in the § 102 traversal above, that the Examiner erred in interpreting the deletions disclosed by the references as the same deletions presently disclosed. In fact, the present inventive methods involve the detection of polymorphisms at the polymorphic site located at nucleotide positions 901-909 of either the wild-type or mutant variant which are represented by instant SEQ ID NO: 1 and 2, respectively. The Applicants have discovered that a polymorphism specifically within this region correlates to various disease predispositions.

Snapir, on the other hand, focuses on the region designated by reference to amino acid residue positions 307-309 in SEQ ID NO: 3 (the wild type), and which corresponds to nucleotide positions 967 to 965 in the wild type allele. Applicants draw the Examiner's attention to the reference SEQ ID NO: 1 and 3, which encode the disclosed "common variant" and the human wild-type, respectively, both of which have the wild-type residue sequence of gaagaggag, (glu glu glu) at positions 901-909, and are therefore not polymorphic at that site as required by instant claim 18.

The secondary claims are directed to genotyping technology and primer selection and do not overcome the deficiency of the primary reference with respect to the polymorphic site limitation.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979).

While Snapir does make a broad disclosure of a deletion of any glu from any position of a 12 glutamine stretch located on the third intracellular loop, the specific polymorphisms employed by the present inventive methods are not disclosed, tested or enabled. The broad

disclosure by Snapir of the deletion of at least one glutamine from a stretch of 12 glutamines encompasses

[12+12x11+12x11x10+12x11x10x9+12x11x10x9x8.....+12x11x10x9x8x7x6x5x4x3x2] = 823,059,744, possible species. That is over 800 million possible species within the genus defined. In contrast, Snapir only specifically discloses or describes a single species within this genus. The Federal Circuit has made it clear that a very broadly disclosed genus of substances fails to render prima facie obvious specific species within its scope. See, e.g. *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994) (holding that a disclosure of millions of compounds did not render obvious a claim to three compounds encompassed by that disclosure); see also *In re Belle* 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) (holding that a DNA sequence would not have been obvious in view of prior art reference suggesting a nearly infinite number of possibilities and failing to suggest why among all those possibilities one would seek the claimed sequence).

Hence, claim 18 is non-obvious and patentably distinct over Snapir in view of Baldwin and Newton and the rejection under 35 U.S.C. § 103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Office Action dated March 11, 2004, and to the rejections of claims 1-22, 30-44 and 63 under 35 U.S.C. §§ 112, second paragraph, 102(e) and 103(a). Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

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